Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Assisted Reproduction Laser Systems

Document issued on: December 28, 2004

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Obstetrics and Gynecology Devices Branch
Division of Reproductive, Abdominal, and Radiological Devices
Office of Device Evaluation

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. Please identify your comments with the docket number listed in the notice of availability that publishes in the *Federal Register* announcing the availability of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document was developed as a special controls guidance to support the classification of assisted reproduction laser systems into class II (special controls). The device is intended to be used to ablate a small tangential hole in the zona pellucida or thin the zona pellucida of the embryo in selected *in vitro* fertilization (IVF) patients with otherwise poor prognosis for successful pregnancy outcome, such as those with advanced maternal age, prior failed IVF, cryopreserved embryos, or abnormal zona pellucida characteristics. This guidance is issued in conjunction with a Federal Register notice announcing the classification of assisted reproduction laser systems.

Following the effective date of the final rule classifying the device, any firm submitting a 510(k) for an assisted reproduction laser system will need to address the issues covered in the special control guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document.

If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the document "A Suggested Approach to Resolving Least Burdensome Issues." It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of assisted reproduction laser systems. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with assisted reproduction laser systems identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.85.)

This special control guidance document identifies the classification regulation and product code for assisted reproduction laser systems (Please refer to **Section 4. Scope)**. In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with assisted reproduction laser systems and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the content requirements of a 510(k) submission. You should also refer to CDRH's **Device Advice** http://www.fda.gov/cdrh/devadvice/ and 21 CFR § 807.87.

As described in the guidance entitled, **The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**, http://www.fda.gov/cdrh/ode/parad510.html, a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a class II special controls guidance document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This

section suggests information to fulfill some of the requirements of section 807.87, as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this special controls guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Please refer to **Section 13** for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

Description of the device and its intended use

We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. Please refer to **Section 5**. **Device Description** for specific information that we recommend you include in the device description for devices of the types covered by this guidance document. You should also submit an "indications for use" enclosure.[1]

Description of device design requirements

We recommend that you include a brief description of the device design requirements.

Identification of the risk analysis method

We recommend that you identify the Risk Analysis method(s) you used to assess the risk profile, in general, as well as the specific device's design and the results of this analysis. (Please refer to **Section 6**. **Risks to Health** for the risks to health generally associated with the use of this device that FDA has identified.)

Discussion of the device characteristics

We recommend that you discuss the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

Description of the performance aspects

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in **Sections 7-12** of this class II special controls guidance document. If you follow a suggested test method, you may cite the method

[1] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[2] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

Reliance on standards

If you choose to rely on a recognized standard for any part of the device design or testing, you may include either a:

- statement that conformance assessment to specified acceptance criteria will be performed before the product is marketed; or
- declaration of conformity to the standard.[3]

Because a declaration of conformity is based on results of a conformance assessment, we believe that you cannot properly submit a declaration of conformity until you have completed your conformance assessment (e.g., the testing that the standard specifies). For more information, please refer to section 514(c)(1)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

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[2] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[3] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification submission for an assisted reproduction laser system.

4. Scope

The scope of this document is limited to the device described below.

Assisted reproduction laser system, regulation number 21 CFR § 884.6200 and product code, MRX.

An assisted reproduction laser system images, targets, and controls the power and pulse duration of a laser beam used to ablate a small tangential hole in, or to thin, the *zona pellucida* of an embryo for assisted hatching or other assisted reproduction procedures.

5. Device Description

We recommend that you identify your device using the regulation and product code described in section **4. Scope** and include:

- laser characteristics (laser type, wavelength, laser class[4], power specifications, pulse duration length, pulse repetition rate)
- design characteristics (circuit diagrams, optical design, filters, lenses, objectives, laser beam collimation, measured focal spot diameter, laser beam controls, alignment setting, laser beam thermal characteristics, pulse repetition limitations, safeguards, etc.)
- beam target position indication system and its validation
- control system, including software algorithm design (description and diagrams)
- description of controls for beam power and pulse duration/repetition rates, as well as repeatability of these parameters
- description of test and validation procedures for factory setting of laser alignment and adjustment for confocality with visible image.

[4]Manufacturers and distributors of products that meet the definition of "electronic product radiation" in section 531 of the Act may be subject to certain provisions of the Act, including the retention of records and submission of product reports to CDRH. The requirements for these products are set forth at 21 CFR 1040.10 and 1040.11. See also CDRH **Device Advice** at http://www.fda.gov/cdrh/devadvice/311.html.

6. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of assisted reproduction laser systems addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risk	Recommended Mitigation Measures
Damage to the Embryo	Section 7. Nonclinical Analysis and Testing Section 10. Software Life Cycle and Risk Management Section 11. Animal Testing Section 12. Clinical Testing Section 13. Labeling
Ineffective Treatment	Section 7. Nonclinical Analysis and Testing Section 10. Software Life Cycle and Risk Management Section 11. Animal Testing Section 12. Clinical Information Section 13. Labeling
Hazards Associated with Electrical Equipment	Section 8. Electrical Equipment Safety
Electromagnetic Interference and Electrostatic Discharge Hazards	Section 9. Electromagnetic Compatibility

7. Nonclinical Analysis and Testing

We recommend that you provide the information described below specific to assisted reproduction laser systems.

Laser interaction with target

We recommend that you provide an analysis of:

- thermal heating of media and embryo as a function of distance from the laser beam associated with different pulse and power settings
- potential for direct irradiation of the embryo

- potential for the formation of plasma or ionized molecules at the target associated with laser treatment
- potential for mutagenic effects on the embryo
- effects of thermal blooming on the embryo
- laser beam energy deposition at target.

We also recommend that you provide a determination of:

- laser beam power and pulse duration capable of achieving a therapeutic effect
- size of the zona pellucida ablated area as a function of beam power and pulse duration
- accuracy and reproducibility of laser treatment
- effect of an underpowered or unfocused laser beam on the target
- safety limits and validation for safety.

Laser beam characteristics

We recommend that you provide an analysis of:

- focal spot dimension
- potential for hot spots or laser beam splashing
- propagation effects, including thermal lensing
- laser beam quality and methods used to measure laser beam quality
- laser beam profile
- maximum safe laser beam power
- maximum safe laser pulse duration
- maximum safe laser pulse repetition rate
- laser beam energy output at objective focus in air over the range of beam power and beam pulse durations to show repeatability of beam energy measurement.

Laser aiming stability

We recommend that you assess the device's aiming stability and describe the:

- target designation procedure
- method of calibration (determining and maintaining aiming stability)
- method of operator testing and confirming aiming stability.

We also recommend that you assess situations/conditions that may lead to reduced laser power output. Examples include bent fiber optic or dust on optical components.

For devices that utilize intermediate optical elements (i.e., beam power transmitted through optical fibers), we recommend that you define the method of beam power feedback control at the objective.

For all assisted reproduction laser systems, we recommend that you provide an analysis of delivered laser power repeatability following multiple disconnections and re-connections of the laser and any associated intermediate optical components.

We also recommend that you validate the compatibility of your assisted reproduction laser system with any inverted microscope listed in the labeling.

8. Electrical Equipment Safety

We recommend that you address the electrical equipment safety, e.g., electrical and mechanical safety, of your device by following **one or more** of the standards identified next or by equivalent methods:

- International Electrotechnical Commission (IEC) 60601-1 Medical Electrical Equipment - Part 1: General Requirements for Safety
- IEC 61010-1 Safety requirements for electrical equipment for measurement, control, and laboratory use – Part 1: General requirements
- Underwriters Laboratory (UL) 60601-1 Medical Electrical Equipment, Part 1: General Requirements for Safety
- American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI) ES-1 Safe current limits for electromedical apparatus (electrical safety only).

The features and design of your device will determine which of the above standards you should use and whether other standards or methods are appropriate in addition to or in place of these standards. The Obstetrics and Gynecology Devices Branch is available to answer any question you may have about which standards are appropriate for your device's features and design.

9. Electromagnetic Compatibility

Electromagnetic compatibility (EMC) encompasses both emissions (interference with other electronic devices) and immunity (interference with device performance created by emissions from other electronic devices). We recommend that you evaluate the EMC of your device as discussed below.

Emissions

EMC testing should demonstrate that the device will not adversely interfere with the performance of other electronic equipment, including emergency radio services, diagnostic devices, and active implantable devices, e.g., pacemakers and defibrillators. Testing should include radio frequency (RF) electromagnetic and conducted emissions.

Immunity

EMC testing should also demonstrate that the device will perform as expected in the presence of other electrical and electronic devices or other sources of electromagnetic disturbance (EMD) in the intended environment of use (immunity). The device should operate in an acceptable manner (few

EMC standards require operation within specification) during and after exposure to various forms of electromagnetic disturbance. Testing should include:

- electrostatic discharge (ESD)
- radiated RF electromagnetic fields
- electrical fast transients and bursts
- surges
- conducted RF electromagnetic energy
- voltage dips, short interruptions, and voltage variations on power supply input lines
- low-frequency magnetic fields.

We recommend that you address the EMC of your device by following **one or more** of these standards or by equivalent methods:

- IEC 60601-1-2 Medical Electrical Equipment - Part 1: General Requirements for Safety; Electromagnetic Compatibility - Requirements and Tests

- IEC 61326 Electrical equipment for measurement, control and laboratory use – EMC requirements.

10. Software Life Cycle and Risk Management

FDA recommends that you submit documentation that provides evidence of proper software life cycle and risk management for all programs associated with the device, including any firmware (embedded software). FDA guidances, **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**, www.fda.gov/cdrh/ode/57.html and **Guidance for Off-the-Shelf Software Use in Medical Devices**, www.fda.gov/cdrh/ode/1252.html, contain information about the documentation recommended. Also, **General Principles of Software Validation**, www.fda.gov/cdrh/comp/guidance/938.html, contains useful information about software life cycle and risk management.

FDA believes that the software used in class II assisted reproduction laser systems meets the definition given in these guidances for a "moderate level of concern." This is because failure to obtain suitable embryos for transfer to the uterus may result in additional rounds of ovarian stimulation and oocyte recovery procedures. Therefore, you should provide documentation recommended for a "moderate level of concern" for the software.

11. Animal Testing

Depending on the similarities and differences of your laser system compared with other legally marketed devices, FDA may recommend animal testing as a part of design validation.[5] If so, we recommend that

[5] Under 21 CFR 820.30(g), you are required to conduct design validation studies under defined operating conditions on initial production units, under actual or simulated use conditions. In accordance with 21 CFR 820.30(j), the results of this testing must be maintained in the design history file.

you test your laser system in an animal embryo model (e.g., bovine, murine or hamster) to demonstrate the capability of the laser for producing known diameter ablated areas in the zona pellucida. We also recommend that this model show that your laser system does not induce thermal or mutagenic damage or lead to an increased implantation failure rate.

12. Clinical Information

In accordance with the Least Burdensome provisions of the Act, the agency will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most assisted reproduction laser systems, FDA may recommend that you collect clinical data for an assisted reproduction laser system with any one of the following:

- design, dissimilar from design previously cleared under a premarket notification
- new technology, i.e., technology different from that used in legally marketed assisted reproduction laser systems
- indications for use dissimilar from assisted reproduction laser systems of the same type.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.

If we recommend a clinical study to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA generally considers laser assisted hatching studies conducted in support of premarket notifications to be significant risk devices, as defined in 21 CFR 812.3(m)(4).[6] In addition to the requirement of having a FDA-approved IDE, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

If we recommend a clinical study, you should design your investigation to demonstrate the substantial equivalence of the device when used as described in the Indications for Use statement. When supported by an adequate scientific rationale, alternatives such as reliance on the literature or use of meta-analyses may be appropriate. We have outlined our recommendations below for each.

For statistical purposes, the study hypothesis should frame the research question in terms of equivalence, non-inferiority, or superiority to the performance of legally marketed predicate devices of this type. We also recommend that you consult a statistician familiar with medical device studies.

[6] Refer to Significant Risk and Nonsignificant Risk Medical Device Studies in **Guidance for Institutional Review Boards and Clinical Investigators** at http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.

Statistical reporting in your premarket notification of clinical study results

We recommend that you define the:

- primary clinical effectiveness endpoints (e.g., implantation rate, clinical pregnancy rate, live birth rate)
- safety endpoints (e.g., congenital anomaly, aneuploidy, miscarriage rate, noticeable laser damage to embryo prior to transfer)
- criteria for determination of clinical effectiveness
- null and alternative hypotheses (in both words and mathematical form)
- equivalence margin
- type I and II error rates
- sample sizes for each device and control group.

We also recommend that you describe the:

- length of follow-up
- type of study design (prospective, retrospective, cross-sectional)
- masking and randomization procedures
- statistical methods used to analyze the clinical data.

If a multi-center study was employed, we recommend that you discuss primary summary statistics, e.g., the difference in two proportions (PD); risk ratio (RR); and odds ratio (OR), and the statistical methods used to pool over multi-center studies.

Reporting results from journal articles

We recommend that you evaluate the consistency of study designs among various studies, such as:

- randomization procedure
- success/failure criteria
- masking
- types of study design (prospective, retrospective, or cross-sectional)
- length of patient follow-up
- patient demographics and clinically important patient covariates (if known)
- patient accountability
- data quality
- types of clinical centers
- patient inclusion/exclusion criteria
- physician experience
- any other factors, if relevant.

We also recommend that you evaluate any potential publication bias.

We recommend that you prepare a homogeneity test in summary statistics (PD, RR, OR) and provide a statistical justification for pooling multi-center studies, i.e., a meta-analysis.

Reporting meta-analyses (for both original clinical studies and journal articles)

If summary data from individual studies are available, we recommend, for each center or each study and for the selected summary statistics (RD, RR, OR, or others, such as the means), that you graphically display the:

- point estimate
- 95% confidence interval
- sample proportion by device and control groups
- width of the 95% confidence interval.

We also recommend that you calculate the appropriately pooled average estimate of summary statistics and the associated 95% confidence interval from various appropriately selected studies.

13. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.[7]

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Under 21 CFR 807.87(e), we recommend submitting clear and concise instructions that delineate the technological features of the specific device and how the device is to be used. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

We recommend that your instructions inform the user of treatment methods that will minimize potential thermal and mutagenic effects on blastomeres near the treatment area, for example, "Administer as few laser pulses as possible at the lowest energy levels possible to achieve prescribed zona drilling or thinning effect" or "Direct the laser beam toward a section of the zona pellucida where the adjacent perivitelline space is widest or next to an area of fragmentation."

We also recommend that your instructions inform the user that a holding pipette is recommended during laser treatment to minimize the risk of embryo movement.

[7] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

User training

We recommend that you develop an operator training protocol that includes several proctored assisted hatching procedures (e.g., utilizing animal embryos). We also recommend that your training protocol include a checklist of topics to be covered during training. Training should ensure operator competency and uniform, optimal treatment technique to safely and effectively use the device for the purposes described in the indication.

Warnings

We recommend that the warnings section of your operator manual address the concerns described below.

Multiple or small openings

Only a single opening should be made in the zona pellucida. Multiple openings or those that are too small may prevent embryo hatching or lead to abnormal development.

Thermal lensing

Thermal lensing is a defocusing of the laser beam as it passes through and heats the medium. Thermal lensing can lead to laser treatment outside of the targeted area, thereby increasing the risk of negative thermal or mutagenic effects on the embryo. (This warning should include information on maximum pulse duration and pulse energy settings that minimize the occurrence of thermal lensing.)

Precautions

We recommend that the precautions section of your operator's manual address the following topics.

Developmental Stage

We recommend that labeling identify the developmental stage of embryos that have been shown to be safely and effectively treated (e.g., 4-8 cell stage) using your device. We also recommend that your labeling reflect that effects on embryos outside of this developmental range have not been evaluated.

Long-Term Follow-Up

We recommend that labeling provide information on the occurrence of birth defects in children derived from laser-hatched embryos. We recommend that you indicate the current knowledge on long-term follow-up data for children derived using this technology.

Patient Brochure

We recommend that you prepare a patient information brochure or fact sheet that addresses the following questions:

- What is assisted hatching?

- What are the different ways of performing assisted hatching?
- Who should have assisted hatching of their embryos?
- What are the risks of assisted hatching using the laser?
- What are the benefits of assisted hatching using the laser?
- What do we know about the health of babies born following laser-assisted hatching?

For information on using a question and answer format and other useful techniques, see Guidance on Medical Device Patient Labeling, http://www.fda.gov/cdrh/ohip/guidance/1128.html.

Microscope Compatibility

We recommend that you provide a list in your operator's manual of inverted microscopes that are compatible with your assisted reproduction laser system.